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Impact of Oral Iron Therapy on Exercise Performance in Adult Iron Depleted Female Athletes

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Abstract

Background: Iron deficiency without overt anemia is a known problem in athletic and physically active women. The exact prevalence in this population in unclear but appears to range from 25-58%. The reasons for this phenomenon are multifactorial and include iron losses, decreased iron absorption and lack of iron consumption in the diet. Iron plays many roles in the human body that can affect exercise performance. Irons main function is to carry and store oxygen throughout the body as a component of hemoglobin and myoglobin. Iron is also a component of cytochromes, in coenzymes in the Krebs cycle and part of the electron transport chain all of which are necessary for endurance activity. The purpose of this review is to evaluate the effects of iron repletion on endurance performance in female athletes who are iron deficient but not anemic.

Methods: An extensive literature search of the following databases, MEDLINE-PubMed, MEDLINE-Ovid, Web of Science, and CINAHL for the terms "sports," "dietary supplements," and "iron" was performed. Results were further limited to articles in the English language and studies performed on human subjects. Further inclusion criteria included active females greater than 17 years of age, premenopausal, iron deficient, oral iron supplementation and studies where exercise performance was evaluated. Exclusion criteria included anemic subjects, parenteral iron supplementation and treatment less than four weeks. All included studies were double blinded and placebo controlled without crossover. The quality of the relevant studies was evaluated using the GRADE criteria .

Results: Two studies met the inclusion criteria and were reviewed. Both studies showed that iron replacement therapy increases iron stores but neither found an improvement in endurance capacity.

Conclusion: Although iron deficiency is a common problem in female athletes and active women, current studies do not show that there is a performance benefit with iron supplementation in women who are not anemic. However, this question is far from answered. Studies employing a more homogenous group of athletes performing a prescribed training program for a period longer than eight weeks are necessary to fully understand the impact of iron supplementation on athletes.

Keywords: iron, sports, dietary supplementation

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Biography

Nicole Knigge completed her undergraduate degree in Kinesiology at Boise State University and became a certified athletic trainer in 2007. She went on to complete a Master of Science degree in Exercise Science from the University of Utah with her thesis work focusing on exercised induced asthma in athletes. She was also the Athletic Trainer for the men's and women's tennis teams at the University of Utah. Nicole later worked with physically active individuals in an outpatient sports medicine clinic focusing on whole wellbeing not just athletic success.

Abstract

Background: Iron deficiency without overt anemia is a known problem in athletic and physically active women. The exact prevalence in this population in unclear but appears to range from 25-58%. The reasons for this phenomenon are multifactorial and include iron losses, decreased iron absorption and lack of iron consumption in the diet. Iron plays many roles in the human body that can affect exercise performance. Irons main function is to carry and store oxygen throughout the body as a component of hemoglobin and myoglobin. Iron is also a component of cytochromes, in coenzymes in the Krebs cycle and part of the electron transport chain all of which are necessary for endurance activity. The purpose of this review is to evaluate the effects of iron repletion on endurance performance in female athletes who are iron deficient but not anemic.
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List of Abbreviations

GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
Hb	Hemoglobin
Hct	hematocrit
HR	Heart Rate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
RDA	Recommended Dietary Allowance
RER	Respiratory Exchange Ratio
sFe	Serum Iron
sFer	Serum Ferritin
sTfr	Serum Transferrin
TIBC	Total Iron Binding Capacity
VO_{2max}	Volume of Maximal Oxygen Consumption
VT	Ventilatory Threshold

Impact of Oral Iron Therapy on Exercise Performance in Iron Deficient Adult Female Athletes

BACKGROUND

Iron deficiency without overt anemia is a recognized problem in physically active women and female athletes. The exact prevalence is unclear but appears to range from 25-58% in the active population and affects upwards of 70% of athletes during the competitive season.[1-3] The reasons for this phenomenon are multifactorial, with iron loss during menses, which can reach 0.6mg/d,[2, 4-8] and inadequate dietary intake being the predominate factors. Other factors include: the use of NSAIDs, prior history of deficiency, recent blood loss, heavy menses, and history of untreated H. pylori infection.[4, 7] Combined with the basal iron needs of the body these factors lead to the recommended dietary allowance (RDA) for iron to be 18mg/d in premenopausal women. Despite this recommendation, data suggest that most women consume only 12-15mg/d.[6, 9] Compounding the matter, many women choose foods low in heme iron, from which up to 10% less iron is absorbed as compared to foods high in heme iron such as meat. Additionally, diets high in fiber also limit iron absorption. These qualities are all found in the low fat, low animal protein, high fiber diet common amongst endurance athletes.[9]

Dietary iron deficiency is compounded with additional losses of iron associated with exercise, especially endurance running. Common avenues of iron loss during activity include: hemolysis (foot strike hemolysis),[1, 2, 4, 5, 7] hematuria from bladder wall trauma or hypoxic damage to the kidneys,[1, 3-6] sweat,[1, 3-7] and GI bleeding from ischemia or unknown etiology.[1, 5-8] These additional losses can bring the iron requirements of a female athlete up to 23mg/d of iron.[6] Along with losses the inflammation associated with activity decreases the ability of the GI tract to absorb iron which can result in low iron stores even with sufficient dietary intake.[3-5, 8]

The importance of iron deficiency in active women cannot be fully appreciated without understanding the functions of iron within the human body. Iron's primary function is to carry and store oxygen throughout the body as a component of hemoglobin and myoglobin. However, unless overt anemia is present and oxygen carrying capacity is compromised, the lesser known functions of iron are likely more important to athletes. Specifically, iron is a component of cytochromes, coenzymes in the Krebs cycle, and part of the electron transport chain,[4, 5, 7-9] which play a major role in the aerobic energy pathways and endurance performance.

Iron indices used to determine iron deficiency include Hb, Hct, sFer, sFe, TIBC, and transferrin saturation. Serum ferritin is the most commonly used index and is often the first indicator of inadequate iron intake.[2] However, the definition of iron deficiency is ambiguous and varies in the literature. A sFer value of 20µg/l is the most common cut-off point in studies investigating iron deficiency but cut-off values across studies range from 10-40µg/l.[1, 3, 4, 7-12] Further, sFer may not be a reliable indicator of iron deficiency as it is an acute phase reactant, with levels influenced by factors other than body iron stores such as inflammation post exercise, liver disease, cardiovascular disease, high alcohol consumption and increasing age.[13] This issue has led some studies to use a transferrin saturation level less than 16% as a definition of iron deficiency.[9] One author has also defined iron deficiency in stages.[7] Stage I corresponds to a decrease in sFer alone, stage II corresponds to decrease in sFer, transferrin saturation, TIBC and sFe and stage III corresponds to true iron deficiency anemia with microcytosis and hypochromia of red blood cells. Another author reports a phenomenon specific to athletes that he defined as "functional anemia." The condition is characterized by normal laboratory ranges for iron and anemia indices, but the ability to further increase the indices thru supplementation, indicates the possibility for inadequate iron stores.[11]

Although there exists substantial inconsistency on the definition of iron deficiency, most authors agree that it is important to rule out all underlying causes of iron deficiency before assuming it is related to activity alone. Even so, many authors still recommend iron supplementation in athletes who sFer values are below 35µg/l.[8, 11, 14] A popular way to do so is to ingest elemental iron, where taking 60mg per day with vitamin C on an empty stomach has been shown to increase iron stores.[6, 8] The sFer level at which to discontinue supplementation is widely unknown, though one author recommends aiming for a sFer of at least 60µg/l.[8] In any case, frequent testing to evaluate sFer levels should be employed during treatment and every six months after treatment has been discontinued to monitor maintenance. Overt anemia's influence on oxygen carrying capacity has obvious effects on aerobic exercise but the consequences of low iron levels are less understood. Thus the purpose of this review is to evaluate the effects of iron repletion on endurance performance in active females who are iron deficient but not anemic.

METHODS

An extensive literature search of the following databases, MEDLINE-PubMed, MEDLINE-Ovid, Web of Science, and CINAHL for the terms "sports," "dietary supplements," and "iron" was performed. Results were further limited to articles in the

English language and studies performed on human subjects. The bibliographies of relevant works were searched for additional sources. Further inclusion criteria included female athletes greater than 17 years of age, premenopausal status, iron deficient, oral iron supplementation and evaluation of exercise performance. Exclusion criteria included studies using anemic subjects, parenteral iron supplementation and a treatment period of less than four weeks. All included studies were double blinded and placebo controlled without crossover. The quality of the relevant studies was evaluated using the GRADE[15] criteria (see Table I).

RESULTS

The initial search yielded 135 articles. After eliminating duplicates, non-English and non-human subjects' articles, 96 articles remained for screening. The articles were screened for relevant material, leaving 21 articles for review. Two articles met all inclusion and exclusion criteria. These articles included female athletes competing in a variety of activities including team sports and individual endurance events. Table II includes a detailed summary of each study. In brief, each study evaluated hematologic indices of iron status and indices of endurance capacity.[16, 17]

In the first study reviewed, Klingshirn et al[17] investigated the effects of iron therapy on endurance capacity in female distance runners with low iron levels. They included 18 female endurance runners with a sFer less than 20µg/l and a Hb greater than 120g/l. Women were excluded if they were current smokers, pregnant within the last year, had significant blood loss in the past six months, were using medication that had the potential to cause bleeding, had an infection within the past month, or a fever in the past two weeks. They supplemented nine women with 50mg of elemental iron twice a day for

8weeks and the other nine received placebo. The subjects were pair matched based on their endurance capacity to help control for variability in physical fitness. Both VO_{2max} and a run to exhaustion test were used to evaluate endurance capacity. The time to exhaustion test was performed on a treadmill at a pace 2-3% slower than each subject's 10K race pace. They were instructed to run until they could no longer maintain that pace. Measurements of exercise capacity included VO_2, RER, HR, RPE and blood lactate levels, while hematologic measures of iron capacity included Hb, Hct, sFe, sFer, TIBC, and percent sTrf saturation. Data regarding training and diet history was collected before each testing session. The authors found that the treatment group had significantly lower TIBC and higher sFer values when compared to the control group after treatment. They noted that the sFer was still low and had a large standard deviation (23.44±6.65) after treatment. No other changes in hematologic parameters were seen. Furthermore no difference in endurance capacity was found between the two groups. Both groups did show an increase in time to exhaustion; however the difference did not achieve statistical significance. Although not statistically significant the authors did note changes in blood lactate levels and RER in the iron treatment group that supported improvement in metabolic function. The authors concluded that there was no improvement in endurance capacity with iron supplementation.[17]

In the second study reviewed, Fogelholm and colleagues[16] investigated the effects of iron repletion on a group of competitive athletes with a sFer less than 25µg/l and a Hb greater than 120g/l. No specific exclusion criteria were reported. The study cohort included 14 women in the treatment group who received 100mg of ferrous sulfate per day for 8 weeks and 17 women in the control who received placebo for the 8 weeks.

Hematologic indices of iron status were evaluated before and after treatment and included Hb, Hct and sFer. Endurance capacity was determined using an incremental cycle ergometer test that evaluated the individuals VO_{2max}, HR and blood lactate levels. The authors found that sFer in the treatment group increased significantly from baseline (from 14μc/l to 26μg/l) as compared to the control group (P=0.001). However, the treatment group showed a non-significant increase in Hb and Hct from baseline while the control group showed a non-significant decrease, resulting in significantly higher post Hb (P=0.001) and Hct (P=0.006) value for the treatment group. Despite this difference, the researchers found no difference in the endurance capacity indices. The authors concluded that iron repletion did not improve endurance capacity in the group of iron depleted females.[16]

DISCUSSION

Importance of Iron Repletion in Athletes

Iron's effects on exercise can be considered twofold. First, if iron levels are low enough to lead to overt anemia, then oxygen carrying capacity will be diminished and therefore VO_{2max} will be reduced. Theoretically, in the absence of anemia no difference in oxygen carrying capacity should exist and therefore no difference in VO_{2max} will ensue. Second, iron integrates with coenzymes and cofactors necessary for aerobic energy production via the Krebs cycle and the electron transport chain. Practically, a decline in the efficiency of these pathways may not have an impact on sedentary individuals. However, endurance athletes rely heavily on aerobic pathways to function at optimal capacity and the lack of coenzymes and cofactors has the potential to severely limit the ability of the athlete to perform aerobic work. Hypothetically this concept holds true but studies to date have found little evidence to support improved efficiency of the aerobic energy systems when mitigating iron deficiency thru supplementation.

Outcomes from Current Research

For the presently reviewed studies[16, 17] both showed an increase in iron stores (as indicated by sFer) following 8 weeks of iron supplementation in iron deficient athletes. One study[16] also showed a decrease in TIBC further indicating an increase in iron stores. In both studies,[16, 17] the effect of increased iron stores on endurance capacity was evaluated using a time to exhaustion protocol and neither study showed a significant improvement between the treatment and control groups at the end of the treatment period.

In addition to measuring time to exhaustion serum lactate, HR and percent VO_{2max} were used to evaluate endurance capacity. If the aerobic energy systems are working at full capacity then the lactate produced by glycolysis will be utilized to produce energy, resulting in a lower serum lactate level. If iron supplementation improved the efficiency of the aerobic energy system a lower serum lactate level should be observed. For the present studies, no significant difference in serum lactate was observed, though one study[17] did show a non-significant decrease in serum lactate in the treatment group. It is possible that a longer treatment period may yield greater changes in serum lactate levels. Heart rate and the percent VO_{2max} used during the endurance test should indicate endurance capacity, with lower values for a given workload being a positive indicator; however, neither study showed a between or within group difference following the treatment period.

Problems with Current Research

There are multiple hypotheses that may explain the lack of intuitive outcomes and consistency within the literature evaluating iron repletion and aerobic activity. One hypothesis is that there is inconsistency in the study populations. In the two studies reviewed,[16, 17] all participants were competitive athletes, but not in the same sport. One study[17] used locally competitive endurance runners whereas the other study[16] also included athletes from team sports such as soccer, baseball, basketball, and handball. In the latter study the majority of the athletes were not participating in endurance sports. As a result the training modality, volume, and intensity vary widely in this study making the subjects dissimilar from one another and from the first study's population of endurance runners.[17]

Another possible hypothesis for inconsistencies is that no standard test for endurance capacity has been established. One study used a cycle ergometer[16] and the other used a motorized treadmill. While the choice in exercise modality may seem unimportant it may have a significant impact if the athlete is inexperienced with the modality or if the modality is different from the activities normally performed by the athlete. Further, both studies used time to exhaustion as a measure of endurance capacity and such a protocol may not reliably measure endurance capacity as many individuals become mentally fatigued before physically fatigued and therefore stop the test prematurely.

Future Research Goals

Further research is needed to truly evaluate the effect of iron supplementation on performance in female athletes. Future studies should employ a larger study population to gain enough statistical power for significant results to have clinically applicable meaning. Further, the test of endurance capacity should be consistent with an individuals' preferred activity and less influenced by mental fatigue.

One study[18] not reviewed because it was performed on non-athletes, used a study methodology more likely to show how iron supplementation would affect athletes. The study used a double blind placebo controlled protocol and took 42 women who were iron deficient but not anemic and supplemented 22 with 20mg of elemental iron per day for two weeks. After two weeks, the women continued their supplementation and began a cycle training program designed by the researchers. Endurance capacity was measured using a 15km cycle time trial. Despite a lower dose of iron supplementation and a shorter treatment period, these authors showed an increase in sFer and a decrease in 15km ride time in the treatment group. They also noted a decrease in serum lactate and a decrease in the percent VO_{2max} used by the treatment group during the time trial.[18].

The overview of the above study is to show that sFer levels may have a larger impact when evaluated in reference to a controlled training program. Investigating the effect of iron supplementation on training volume and intensity during a controlled training program in athletes will provide valuable information regarding the utility of treating non anemic iron deficient athletes.

CONCLUSION

Although iron deficiency is a common problem in female athletes and active women, current studies do not show that there is a performance benefit with iron supplementation in women who are not anemic. However, this question is far from answered. Studies employing a larger and more homogenous group of athletes performing a prescribed training program for a period longer than eight weeks are necessary to fully understand the impact of iron supplementation on athletes.

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Table I. Characteristics of Reviewed Studies

Study	Year	Llimitations of Methodology	Indirectness	Imprecision	Inconsistency	Publication Bias Likely	Quality
Klingshirn et al [17]	1992	serious[a]	not serious	serious[b]	not serious	no bias likely	low
Fogelholm et al[16]	1992	very serious[a,c]	not serious	serious[b]	not serious	no bias likely	very low

a. short duration of trial
b. small sample size
c. lack of exclusion criteria failed to fully account for possible confounders

Table II. Summary of Findings

Study	Year	Subjects		Inclusion Criteria	# Treatment	# Placebo	Intervention		Testing	Outcome Measure	Finding	Conclusion
		Descriptors	Age (years)				Supplement	Length				
Klingshirn et al 1992[17]	1992	female endurance runners	22-39	Hb>120 sFer < 20	9	9	100mg elemental iron	8 weeks	hematologic tests	iron	no difference	iron repletion does not improve endurance capacity
										TIBC	significant ↓	
										Transferrin saturation	no difference	
										Ferritin	significant ↑	
										Hemoglobin	no difference	
										Hematocrit	no difference	
									VO2max test	VO2max	no difference	
									endurance capacity test	time to exhaustion	no difference	
										blood lactate	non significant ↓	
										RER	non significant ↓	
Fogelholm et al 1992[16]	1992	female athletes	17-31	Hb >120g/L sFer <25mcg/L	14	17	100mg ferrous sulfate	8 weeks	hematologic tests	ferritin	significant ↑ between & within groups	iron repletion does not improve endurance capacity
										Hemoglobin	significant difference between group	
										Hematocrit	signficant difference between group	
									VO2max test	VO2max	no difference	
									endurance capacity test	time to exhaustion	no difference	
										blood lactate	no difference	
										HR	no difference	